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# Evaluation of trimethylamine n-oxide levels in pleural effusion



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**Abstract**
Aim: Although many parameters have been studied for the diagnosis, follow-up and treatment of pleural fluid, the level of Trimethylamine-N oxide (TMAO) has not been reported so far. In our study, by investigating the TMAO levels in the effusion fluid of patients with pleural effusion, we aimed to report a mean pleural fluid TMAO value and its relationship with diseases.
Material and Methods: The pleural fluids of 49 patients who were treated in the last year were included in the study. The patients were divided into two groups as transudate (Group 1) and exudate (Group 2) and the results were compared.
Results: The mean age of the patients was 65.77 ± 15.13 years. The mean TMAO value of the patients was found to be 0.43 ± 0.12, which is lower than normal TMAO plasma values. When groups 1 and 2 were compared, the results of Group 1 were found to be significant in terms of the mean PLT and CRP values ($p < 0.05$). Although trimethylamine-N oxide concentrations were low in normal plasma, no significant difference was found when the two groups were compared ($p = 0.9124$).
Discussion: Although the serum Trimethylamine-N oxide levels of the patients were reported to be high for most of these reasons, no elevation of TMAO was observed in the pleural effusion fluids of the disease groups in our study. On the contrary, a mean value well below the serum TMAO values of these patients was obtained. The pleural fluid TMAO value was determined as 0.43 ± 0.12. We are of the opinion that even if the serum TMAO values that cause pleural effusion are high in the disease groups, this elevation does not pass into the pleural space.

**Keywords**
Effusion, Pleura, Trimethylamine-N oxide

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## Introduction

Pleural effusion is an excessive accumulation of fluid between the layers of the pleurae. It is a symptom not only of the pleura, but also lung and/or extrapulmonary local-systemic diseases. Its prevalence is 320/100000. Although it is seen equally in both gender, its etiology is different according to gender. Pleural effusions are divided into two groups as transudate and exudate. It can develop due to many benign and malignant diseases. Two-thirds of malignant pleural effusions occur in women. It is especially related to breast and gynecological cancers. On the other hand, effusions due to malignant mesothelioma and pancreatitis are more common in men [1].

The main causes of effusions are heart failure, liver diseases, parapneumonic effusions, pulmonary embolism, pericardial diseases, coronary by-pass surgery, autoimmune rheumatic diseases, chylothorax/pseudochylothorax, hemothorax, pancreatic diseases, kidney diseases, and tuberculosis. According to the underlying diseases, the results of many cytological, microbiological, biochemical and immunological parameters have been reported in effusion fluids, but the level of trimethylamine-N oxide (TMAO) has not been reported so far [1].

Trimethylamine-N oxide (TMAO) is a metabolite formed as a result of a high-protein diet. Trimethylamine (TMA) is formed as a result of the metabolism of L-carnitine, choline and phosphatidylcholine by intestinal microorganisms. Trimethylamine is converted to TMAO in the liver. As the plasma TMAO level increases, the risk of malignancy, inflammatory diseases, and major cardiovascular events also increases [2]. Its high level causes colorectal cancer, inflammatory bowel disease, and atherosclerosis [3]. A relationship has been found between trimethylamine-N oxide elevation and many diseases, but it has not been studied in pleural effusions. In our study, the TMAO levels in the effusion fluid of patients with pleural effusion were investigated and we aimed to report a mean pleural fluid TMAO value and the relationship of this value with diseases.

## Material and Methods

### *Patients*

The pleural fluids of 49 patients treated for pleural effusion between January 2020 and March 2021 were included in the study. The study was approved by the Ethics Committee (28.04.2021-1941).

### *Procedures*

Blood samples were taken from the patients for routine whole blood, biochemistry and C-reactive protein analysis. Fluids obtained for trimethylamine-N oxide measurement were taken by thoracentesis or tube thoracostomy, pleurocan or thoracotomy procedures. The patients were divided into two groups (Group 1: transudate, Group 2: exudate) according to their fluid properties. Demographic and laboratory values of each group were recorded.

Pleural fluids were stored in the freezer at -17.7°C until TMAO analysis. Human TMAO sandwich ELISA kit with LOT number 202104 produced by SunRed Biotechnology company was used in the study. All procedures were performed according to the protocol of the kit. TMAO levels in effusion fluids were measured at 450 nm using the Skanlt RE 5.0 program on a Thermo Scientific ELISA reading device. As a result of the reading, the concentration and OD values of the standard graphics and samples were obtained.

Age, gender, symptoms, laboratory values and underlying diseases of the patients were investigated. The total demographic characteristics and mean laboratory values of the patients were obtained. Since the study was conducted with effusion fluids and it was not possible to create a control group, the results were compared with normal blood values of TMAO and the results determined in previous studies. In addition, different values were also compared between groups and within the same group. Their significance was analyzed.

### *Inclusion and exclusion criteria*

Pleural fluids (hemothorax) due to trauma were excluded from the study.

### *Statistical analysis*

IBM SPSS Statistics version 22.0 was used for data analysis. Continuous variables were expressed as mean±standard deviation, while categorical variables as number-ratio. Homogeneity analysis of variances was performed using Levene's test ($p>0.05$). The Shapiro Wilk test was used to evaluate normality ($p>0.05$). Results were evaluated with the Mann Whitney-U and Student's t tests. $P<0.05$ was considered significant.

## Results

A total of 49 patients were included in the study. Thirty (61%) patients were male, while 19 (39%) were female. The mean age of the patients was 65.77 ± 15.13 years. The mean WBC of the patients was found to be 8.76 ± 3.01, RBC was 4.21 ± 0.66, HBG was 11.92 ± 2.33, HCT was 37.41 ± 5.20, PLT was 268.96 ± 116.89, ALB was 3.57 ± 0.68, total protein was 6.53 ± 5.82, glucose was 144.17 ± 65.255, urea was 62.11 ± 35.23, creatinine was 1.88 ± 0.44, CRP was 47.11 ± 39.60, and TMAO was 0.43 ± 0.12. Considering the laboratory values of

**Table 1.** Demographic distribution and laboratory results of Group 1 and Group 2 patients.

| Variables | Group 1 | Group 2 | The z-score | P value |
|---|---|---|---|---|
| Male/Female | 11/4 | 19/15 | - | 0,1425 |
| Average age | 67,66±14,06 | 64,94±15,70 | - | - |
| Average WBC | 7,96±1,27 | 9,56±4,75 | 0,05781 | 0,95216 |
| Average RBC | 4,20±0,5 | 4,23±0,82 | -0,3122 | 0,75656 |
| Average HBG | 12,19±1,53 | 11,65±3,13 | -0,89759 | 0,36812 |
| Average HCT | 38,12±3,64 | 36,71±6,77 | -0,87602 | 0,37886 |
| Average PLT | 202,6±100,26 | 335,32±133,52 | 3,39496 | 0,0007 |
| Average ALB | 3,63±0,79 | 3,52±0,57 | -0,67075 | 0,50286 |
| Average T-protein | 6,90±1,32 | 6,16±09 | -1,28149 | 0,20054 |
| Average glucose | 169,2±94,63 | 119,14±35,88 | -1,7246 | 0,08544 |
| Average urea | 66,22±29,05 | 58±41,41 | -1,51943 | 0,12852 |
| Average creatinine | 2,67 | 1,10±0,89 | -1,3659 | 0,17068 |
| Average CRP | 11,36±19,48 | 82,86±59,73 | 4,87793 | 0,0001 |
| Average TMAO (ng/ml) | 0,41±0,07 | 0,46±0,18 | 0,10792 | 0,9124 |

WBC; White blood cell, RBC; White blood cell, HBG; Hemoglobin, HTC; Hematocrit, PLT; Platelet, ALB; Albumin, CRP; C-reactive protein, TMAO; Trimethylamine-N oxide, Tprotein; Total protein

**Table 2.** Etiological causes in patients in Group 1 and Group 2.

| Disease | Group 1 (n: 15) | Group 2 (n: 34) |
|---|---|---|
| Infection | 5 | 6 |
| CRF | 5 | 0 |
| CHF | 5 | 0 |
| Lung adeno ca | 0 | 3 |
| Lung squamous ca | 0 | 4 |
| Endometrium | 0 | 1 |
| Chronic myelocytic leukemia | 0 | 1 |
| Malignant melanoma | 0 | 1 |
| Breast ca | 0 | 4 |
| Mesenchymal tumor | 0 | 1 |
| Pleural mesothelioma | 0 | 4 |
| Gastric | 0 | 4 |
| Multiple myeloma | 0 | 2 |
| Non-Hodgkin's lymphoma | 0 | 1 |
| Ovarian | 0 | 1 |
| Pancreatic ca | 0 | 1 |

CHF; Chronic heart failure, CRF; Chronic renal failure, N; Number, Ca; Cancer

**Table 3.** Mean TMAO values of patients in Group 1 and Group 2

| Causes of effusion in groups | TMAO of the groups (ng/ml) | The z-score | P value |
|---|---|---|---|
| Infection (G2, n:6)/Malignancy (G2, n: 28) | 0,46±0,22/0,46±0,18 | -0,16892 | 0,86502 |
| Infection (G1, n: 5)/Malignancy (G2, n: 28) | 0,40±0,08/0,46±0,18 | 0,36662 | 0,71138 |
| CHF (G1, n: 5)/Malignancy (G2, n: 28) | 0,43±0,05/0,46±0,18 | -0,43815 | 0,65994 |
| CRF (G1, n: 5)/Malignancy (G2, n: 28) | 0,40±0,08/0,46±0,18 | -0,11624 | 0,90448 |
| Infection (G1, n: 5)/Infection (G2, n: 6) | 0,40±0,08/0,46±0,22 | 0,36266 | 0,71884 |
| CHF (G1, n: 5)/Infection (G2, n: 6) | 0,43±0,05/0,46±0,22 | -0,03297 | 0,97606 |
| CRF (G1, n: 5)/Infection (G2, n: 6) | 0,40±0,08/0,46±0,22 | -0,09891 | 0,92034 |
| CHF (G1, n: 5)/Infection (T, n: 5) | 0,43±0,05/0,40±0,08 | 0,75593 | 0,44726 |
| CRF (G1, n: 5)/Infection (T, n: 5) | 0,40±0,08/0,40±0,08 | -0,52915 | 0,59612 |
| CRF (G1, n: 5) / CRF (G1, n: 5) | 0,40±0,08/0,43±0,05 | 0,30237 | 0,76418 |

CHF; Chronic heart failure, CRF; Chronic renal failure, TMAO; Trimethylamine-N oxide, G; Group, T; Transude N; Number

the patients, it was observed that the TMAO values were lower than the normal blood values.

The mean age of patients in Group 1 (transudate, n; 15) was 67.66 ± 14.06. Of the patients, 11 (73%) were male, while 4 (27%) were female. The mean WBC was found to be 7.96 ± 1.27, RBC was 4.20 ± 0.5, HBG was 12.19 ± 1.53, HCT was 38.12 ± 3.64, PLT was 202.6 ± 100.26, ALB was 3.63 ± 0 .79, total protein was 6.90 ± 1.32, glucose was 169.2 ± 94.63, urea 66.22 ± 29.05, creatinine was 2.67, CRP was 11.36 ± 19.48, and TMAO was 0.41 ± 0.07.

The mean age in Group 2 (exudate, n; 34) was 64.94 ± 15.70 years. Of the patients, 19 (56%) were male, while 15 (44%) were female. The mean WBC was found to be 9.56 ± 4.75, RBC was 4.23 ± 0.82, HBG was 11.65 ± 3.13, HCT was 36.71 ± 6.77, PLT was 335.32 ± 133.52, ALB was 3.52 ± 0.57, total protein was 6.16 ± 09, glucose was 119.14 ± 35.88, urea was 58 ± 41.41, creatinine was 1.10 ± 0.89, CRP was 82.86 ± 59.73, and TMAO was 0.46 ± 0.18 (Table 1).

When groups 1 and 2 were compared, Group 1 was found to be significant in terms of mean PLT and CRP values ($p < 0.05$). No significant difference was found when trimethylamine-N oxide concentrations were compared (Table 2) ($p = 0.9124$).

The most common underlying diseases in Group 1 were infection (n; 5, 33%), chronic renal failure (n; 5, 33%), and congestive heart failure (n; 5, 33%), while they were infection (n; 6, 18%) and malignancy (n; 28, 82%) in Group 2. The distribution of patients with malignancy was lung adenocarcinoma in 3 (11%), lung squamous cancer in 4 (14%), endometrial cancer in one (4%), chronic myelocytic leukemia in one (4%), malignant melanoma in one (4%), breast cancer in 4 (14%), mesenchymal tumors in one (4%), pleural mesothelioma in 4 (14%), gastric cancer in 4 (14%), multiple myeloma in two (7%) non-Hodgkin's lymphoma in one (4%), ovarian cancer in one (4%), and pancreatic cancer in one (4%) (Table 2).

Mean TMAO values of patients in Group 1 with infection, chronic renal failure (CHF), and congestive heart failure (CRF) were 0.40±0.08, 0.43±0.05, and 0.40±0.08, respectively. In addition, the mean TMAO values were 0.46±0.22 and 0.46±0.18 in patients in Group 2 with infection and malignancy, respectively. TMAO values related to diseases were not found to be statistically significant. The mean values were below normal blood values (Table 3).

The most common complaints in both groups were pain and shortness of breath. It was observed that all patients were diagnosed with computed tomography of the thorax, and chest radiography was less preferred. Both groups continued to be given oxygen, bronchodilator, mucolytic expectorant, and drugs used for chronic diseases before.

## Discussion

Normally, there is 0.1-0.2 ml/kg of pleural fluid, which acts as a slider between the pleural leaves in both hemithoraxes. This corresponds to 10-15 ml of fluid between the pleural leaves in each hemithorax. In fact, the amount in question is the remainder of a 5-10 liter fluid cycle that takes place within 24 hours between the pleural leaves. In cases that adversely affect this cycle, pleural effusion occurs. It is seen equally in both genders. Cough caused by pleural effusion is mild and non-productive. Chest pain is of sharp-pounding or blunt type and increases with deep inspiration. Diagnosis is made by physical examination, posteroanterior/lateral chest X-ray, ultrasonography, and computed tomography [1]. In our study, the number of male patients (n: 30) was higher, the most common symptom was chest pain and shortness of breath, and the most commonly used diagnostic method was computed tomography of the thorax.

The easiest way to sample a pleural effusion is thoracentesis. Biochemical analysis should be performed for the characteristics of the effusion. Therefore, blood is drawn simultaneously with the pleural fluid. Transudate/exudate differentiation is made by investigating the pleural fluid and serum protein, albumin and LDH ratios, which are expressed as Light's criteria [4]. This distinction is extremely important in terms of differential diagnosis and treatment. In our study, the number of patients with transudative fluid was 15, while the number of patients with exudative fluid was 34. While the number of diseases causing transudative fluid formation was equal, most of the diseases causing exudative fluid formation were malignancies.

Glucose, triglyceride, cholesterol, pH, hematocrit, adenosine

deaminase, amylase, creatinine, NT-pro BNP levels, and the levels of many markers according to related diseases have been studied in pleural effusions [4, 5]. In addition, microbiological, immunological, and cytological studies related to the fluid have also been reported [5-7]. In our study, the mean pleural fluid TMAO value, which has not been reported so far, was determined as 0.43 ± 0.12 without distinction between transudate and exudate.

Some metabolites formed as a result of a high-protein diet cause malignancy, inflammatory bowel diseases, and cardiac diseases. One of these metabolites is a trimethylamine-N oxide (TMAO). Trimethylamine-N oxide consists of choline, lecithin and L-carnitine, and trimethylamine (TMA) produced by the gut microbiota [2, 8,]. The TMAO is then either transported to tissues for accumulation or excreted by the kidney [2, 3, 9]. Plasma TMAO levels vary widely among individuals. Circulating TMAO levels are determined by a number of factors including diet, gut microbial flora, liver flavin monooxygenase enzymes, and kidney function [10]. The heritability of trimethylamine-N oxide has been reported in studies [11]. In a study conducted on healthy subjects, fasting plasma TMAO levels were measured and a median concentration of 3.45 μM (range 2.25-5.79) was reported, which did not differ by gender [11]. Although there were no serum values in our study, the mean pleural fluid TMAO value was 0.43 ± 0.12.

Studies of the pharmacokinetics and renal clearance of TMAO in healthy human subjects have shown that TMAO has a small volume of distribution (about half that of urea) but a higher renal clearance compared to urea and creatinine [12]. Missailidis et al. measured the plasma concentration of TMAO in 80 controls and 179 chronic kidney disease patients and reported that high TMAO levels were strongly associated with the degree of renal function [13]. Kaysen et al. measured serum TMAO levels in 235 hemodialysis patients and reported that serum TMAO concentrations in these patients were higher than in those with normal or near-normal kidney function [8]. Bain et al. found that TMA and TMAO levels in plasma before dialysis (1.39±0.483, 99.9 ± 31.9 mM, respectively) were higher than in healthy subjects (0.418 ± 0.124 and 37.8 ± 20.4 mM, respectively) [14]. In our study, the mean pleural fluid TMAO in patients with CRF was 0.40±0.08, which was found to be much lower than the serum TMAO values of patients with kidney disease in other studies.

In a study with 3903 patients, high plasma levels of choline and betaine were associated with a poor prognosis for cardiovascular risk factors. However, high choline and betaine levels were reported to be associated with the risk of future major cardiac events, only with concomitant increased TMAO levels [15]. In another study, TMAO levels were increased in patients with stable heart failure, and high levels were associated with an increased risk of death [16]. Therefore, substantial evidence has suggested that high TMAO levels are associated with cardiovascular disease (CVD). Mueller et al. measured plasma concentrations of TMAO, betaine, and choline in a cohort of 339 patients who underwent coronary angiography and noted that TMAO plasma concentrations were higher in diabetics compared to euglycemic patients [17]. Stubbs et al. reported that high concentrations of TMAO were an independent predictor of coronary atherosclerosis and increased long-term mortality independent of traditional cardiac risk factors [18]. In our study, the mean pleural fluid TMAO in patients with CHF was 0.43 ± 0.05, which was found to be much lower than the serum TMAO values of patients with heart disease in other studies.

In a study conducted with 345 patients with ischemic stroke, serum levels of TMAO ranged from 0.5 to 18.3 μM, with a median value of 5.8 (IQR, 3.3–10.0) μM. In the control group of this study, the mean value was found to be 3.9 (IQR, 2.6–6.1 μM) [19]. In our study, the mean value was found to be far below the serum value of the control group of that study. In a study of 644 cases with colorectal cancer, it was reported that the risk of colorectal cancer was 3 times higher in men with high serum choline compared to those with low serum choline [20]. In our study, the mean pleural fluid in patients with malignancy was 0.46 ± 0.18, which was found to be much lower than the serum TMAO values of the patients in other studies.

## *Conclusion*

Pleural effusions can develop due to many reasons. Although the serum Trimethylamine-N oxide levels of the patients were reported to be high for most of these reasons, no elevation in TMAO in pleural effusion fluids was observed in the disease groups in our study. On contrary, a mean value obtained was significantly lower than the serum TMAO values of these patients. The pleural fluid TMAO value was determined as 0.43 ± 0.12. We are of the opinion that even if the serum TMAO values are high in the disease groups that cause pleural effusion, this elevation does not pass into the pleural space.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

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***Conflict of interest***

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